

REMARKS

Applicants respectfully request reconsideration of the present application in view of the following commentary.

I. Status of the Claims

Claims 25-35 and 76-86 were cancelled previously. Claims 2, 45 and 59 have been amended for greater clarity. Because no new matter is introduced, Applicants respectfully request entry of this amendment. Upon entry, claims 1-24, 36-75 and 87-90 will be pending.

II. Statement of the Substance of the Interview

Applicants thank Examiner Susan Tran for the courtesies extended during the in-person interview with Applicants' representatives, Ms. Andrea Small and Mr. Christian Bauer, on April 16, 2008. During the interview, Applicants' representatives pointed out that the primary reference, Liversidge, discloses the genus of anti-diabetic drugs in a laundry list of active agents but fails to disclose the claimed nanoparticulate glipizide compositions. Examiner Tran agreed to consider Applicants' response to the Office Action upon submission.

III. Rejection of Claims under 35 U.S.C. § 103(a)

A. Liversidge and Kuczynski

Claims 1-8, 10, 11, 13-15, 17-24, 40-43, 45-50, 52, 53, 55-65, 67, 68, 70-75 and 87-90 are rejected under 35 U.S.C. § 103(a) for alleged obviousness over U.S. Patent No. 5,145,684 to Liversidge et al. ("Liversidge"), in view of U.S. Patent No. 5,024,843 to Kuczynski et al. ("Kuczynski"). Applicants respectfully traverse the rejection.

The Examiner has the initial burden of showing that the cited references establish a *prima facie* case of obviousness. See *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). In the present case, the Examiner has failed to meet this initial burden as the Examiner has not

provided a motivation to combine the references or any evidence of a reasonable expectation of success of modifying or combining the prior art references.

(i) **Motivation of combining the teachings of Liversidge and Kuczynski is lacking.**

To reject a claim on the basis of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *See in Re Kahn*, 441 F.3d 977, 78 USPQ2d 1329 (Fed. Cir. 2006). “While the [U.S. Supreme] Court recently rejected a rigid application of the teaching, suggestion, or motivation (“TSM”) test in an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness determination.” *Takeda Chemical Industries, Ltd. V. Alphapharm Pty., Ltd.*, ---F.3d---, 2007 WL 1839698 (Fed. Cir. 2007) (citing *KSR Intl. Co. v. Teleflex Inc.* 127 S.Ct. 1727, 1741, 82 USPQ2d 1385, 1396 (2007)).

Liversidge relates to a composition comprising drug particles having an effective average particle size of less than about 400 nm and a surface modifier adsorbed on the surface of the drug particles. Liversidge further discloses, in a laundry list of drug substances, that anti-diabetic agents may be used in the context of the invention. Liversidge does not disclose a nanoparticulate glipizide composition, as claimed in the present application.

The Examiner acknowledges that “Liversidge does not explicitly teach the claimed active, such as glipizide” (Office Action, page 3, first full paragraph), but relies on the alleged teaching of the secondary reference, Kuczynski, to bridge the gap. Kuczynski’s disclosure is irrelevant to a nanoparticulate active agent composition. Rather, Kuczynski relates to a controlled release dosage form comprising granules of glipizide. *See* column 1, lines 57-60 and Examples 1 and 2.

The Examiner did not clearly articulate any motivation to combine the teachings of the cited references, but advanced a rationale that “it would have been obvious to one of ordinary skill in the art to select glipizide...[(a)] because Kuczynski teaches [that] glipizide is a known antidiabetic agent in [the] pharmaceutical art, and [(b)] because Kuczynski teaches glipizide is odorless and advantage antidiabetic agent useful for the treatment of diabetes” (Office Action, page 3, second full paragraph).

Point (a) merely provides evidence that glipizide is one of thousands of known antidiabetic agents in the pharmaceutical art. Point (b) is irrelevant to the preference for glipizide as an antidiabetic and is insufficient to support a reason for combining the references, because neither of the references teaches that the properties of being “odorless and advantage” distinguishes glipizide as a preferred antidiabetic agent over other known antidiabetic agents.

As noted above, Kuczynski relates to a composition comprising granules of rather than nanoparticulate glipizide. A “granule” of an active agent is significantly different from a “nanoparticulate” active agent, both in terms of physical and biological properties. Specifically, the physical differences are evidenced by the definition in the online Wikipedia encyclopedia (printed on June 19, 2008; submitted herewith as exhibit A), “in pharmaceutical terms, a granule is small particles gathered into a larger, permanent aggregate in which the original particles can still be identified.” “A specified particle size of [a granule is] 2-4 millimetres,” which is 2000- to 4000-fold larger than the particle size of the claimed glipizide composition.

The primary reference, Liversidge, discloses a composition comprising a drug substance having an effective average particle size of less than about 400 nm and a surface modifier associated with the surface of the drug particles (column 2, lines 50-60; column 4, lines 28-30). Liversidge further demonstrates by comparative examples A-F that not every combination of surface stabilizer and drug substance will produce a stable nanoparticulate active agent (columns 14-15). Informed by Liversidge’s “no guarantee of success” in obtaining a stable nanoparticulate active agent composition and limited by the lack of specific disclosure of antidiabetic drugs, one

skilled in the art would not have been motivated to combine the teaching of Kuczynski with that of Liversidge to arrive at the claimed invention. This is because Kuczynski does not even provide the slightest suggestion regarding reducing the particle size of glipizide, which is the requisite of a stable nanoparticulate glipizide composition. On the contrary, Kuczynski's composition comprises granules of glipizide, which are significantly larger than the effective average size of Liversidge's drug particles.

Because the Examiner has not advanced any credible reason why Liversidge and Kuczynski can be properly combined in a manner so as to render obvious the claimed invention, the claims are patentable over the cited references for this reason alone.

(ii) **Evidence of reasonable expectation of success is lacking.**

In addition to providing a motivation to combine the cited teachings, the Examiner must also demonstrate that there is a reasonable expectation that the suggested modifications to or combination of the prior art references will be successful. *See In re Merck & Co., Inc.*, 800 F.2d 1091, 213 USPQ 375 (Fed. Cir. 1986). In the present case, in an attempt to establish such a "reasonable expectation of success", the Examiner has applied an "obvious to try" rationale that is improper under the statute and governing case law.

The U.S. Supreme Court's decision, *KSR International Co. v. Teleflex Inc.*, prompted a reconsideration of the obvious-to-try rationale, *i.e.*, positing the obviousness choosing from a finite number of identified, predictable solutions with a reasonable expectation of success. *See* the EXAMINATION GUIDELINES FOR DETERMINING OBVIOUSNESS UNDER 35 U.S.C. §103..., published in the *Federal Registrar*, Vol. 72, No. 195 (October 10, 2007), hereafter "the Guidelines." Pursuant to the Guidelines, an examiner seeking to advance an obvious-to-try rationale is obliged to articulate:

- (1) a finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem;

- (2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem;
 - (3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and
 - (4) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.
- If any of these findings cannot be made, then this rationale is unavailable to validate a conclusion that the claim(s) in question would have been obvious, within the meaning of Section 103.

In the present instance, the Examiner has failed to meet the initial burden, pursuant to the Guideline requirements, of establishing a *prima facie* case of obviousness. This is because, contrary to the Examiner's contention, there was no predictability in the field of nanoparticulate active agent compositions in view of an enormous number of anti-diabetic agents involved and there was no reasonable expectation of successfully obtaining a stable nanoparticulate glipizide composition.

(1) The Immensity of the Genus of Anti-diabetic Agents

Anti-diabetic agents are an immense group of drugs and chemical compounds that differ in their chemical structure, physical properties, therapeutic effects and adverse reactions. Anti-diabetic agents do not constitute a small recognizable class of compounds with common properties. Thus, the mere disclosure of the genus of anti-diabetic agents in the primary reference does not render obvious each and every anti-diabetic agent.

As submitted in the Appeal Brief filed on October 31, 2007, Applicants marshaled a number of pre-filing publications in support of the state of the art at the time of the invention. In summary, an overwhelming number of anti-diabetic agents was available before filing of the present application. The genus of anti-diabetic agents includes, among others, (1) biguanides, such as metformin and phenformin; (2) glucosidase inhibitors, such as precose, acarbose,

miglitol, emiglitate, voglibose and camiglibose; (3) insulins, insulin analogues and insulin secretagogues; (4) meglitinides, such as nateglinide, repaglinide and mitiglinide; (5) sulfonylureas, such as acetohexamide, chlorpropamide, gliclazide, glibenclamide, glimepiride, glipizide, glyburide, tolazamide and tolbutamide; (6) biguanide/glyburide combinations, such as Glucovance®TM; (7) thiazolidinediones, such as troglitazone, rosiglitazone and pioglitazone; (8) PPAR-alpha agonists; (9) PPAR alpha/gamma dual agonists; (10) glycogen phosphorylase inhibitors; (11) RXR agonists; (12) imidazolines; (13) fatty acid oxidation inhibitors; (14) inhibitors of fatty acid binding protein (aP2); and (15) SGLT2 inhibitors.

The contemporaneous art was hardly one characterized by “a finite number of identified, predictable potential solutions.” To the contrary, one of ordinary skill in the art would have had no reason to expect that a stable nanoparticulate active agent composition could have been successfully obtained for each drug that falls within the broad spectrum of anti-diabetic agents, based on the general disclosure of anti-diabetic agents in the primary reference. In fact, as detailed below, the cited art, as well as the inventors’ own disclosure, demonstrates that success in obtaining the claimed invention was unexpected.

(2) Unpredictability of Formulating Glipizide into Stable Nanoparticulate Compositions

As taught by Liversidge, not every combination of surface stabilizer and active agent will result in a stable nanoparticulate active agent composition. For instance, comparative examples A-F of Liversidge demonstrate that some combinations of drugs and surface stabilizers result in undesirable aggregation of the drug particles. *See* Liversidge, columns 14-15. Accordingly, the present invention is directed to the surprising discovery that nanoparticulate glipizide compositions can be made” (page 23, paragraph [0103]).

In spite of the contravening evidence, the Examiner persistently rejected the claims on the grounds of obviousness over Liversidge and Kuczynski. Applicants respectfully urge the

Examiner to consider the totality of the record, including the state of the art at the time of filing, as well as the teachings of the cited art and the disclosure of the present application.

In view of the foregoing, withdrawal of the rejection under Section 103(a) over Liversidge and Kuczynski is warranted.

B. Liversidge and Kuczynski in view of Various Tertiary References

Claim 16 is rejected under 35 U.S.C. § 103(a) for alleged obviousness over Liversidge in view of Kuczynski and GB 2316316 to Baralle et al. ("Baralle"). Applicants respectfully traverse the rejection.

Claims 36-39 are rejected under 35 U.S.C. § 103(a) for alleged obviousness over Liversidge, in view of Kuczynski and U.S. Patent No. 4,389,397 to Lo et al. ("Lo"). Applicants respectfully traverse the rejection.

Finally, claims 9, 12, 44, 51, 54, 66 and 69 are rejected under 35 U.S.C. § 103(a) for alleged obviousness over Liversidge, in view of Kuczynski and PCT Publication No. WO 98/07414 by Parikh et al. ("Parikh"). Applicants respectfully traverse the rejection.

All of these rejections are based on the common references, Liversidge and Kuczynski, which are discussed *supra*. Because either the rejected claims are dependent from a non-obvious base claim or the additional cited art does not compensate for the deficiencies of Liversidge and Kuczynski, Applicants respectfully request withdrawal of the rejections.

CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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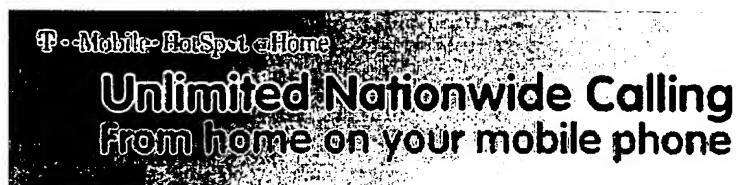
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Granule is a generic term used for a small particle or grain. The generic term is used in a variety of specific contexts.

Granule (solar physics), visible structures in the photosphere of the Sun arising from activity in the Sun's convective zone

Granule (cell biology), any of several submicroscopic structures, some with explicable origins, others noted only as cell type-specific features of unknown function

"Azurophil granule", a structure characteristic of the azurophil eukaryotic cell type

"Chromaffin granule", a structure characteristic of the chromophil eukaryotic cell type

Martian spherules, spherical granules of material found on the surface of the planet Mars

A specified particle size of 2-4 millimetres (-1 - -2 on the ϕ scale)

In pharmaceutical terms, a granule is small particles gathered into a larger, permanent aggregate in which the original particles can still be identified

In computing: a granule is a unit of contiguous (adjacent/bordering) virtual memory allocation.

For the treatment of memory granules in the Oracle database, see granule (Oracle DBMS).

See also

Granular material

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